(2019). Assessment of Brain Injury and Brain Volumes after Posthemorrhagic Ventricular Dilatation: A Nested Substudy of the Randomized Controlled ELVIS Trial. *Journal of Pediatrics*, *208*, 191-197.e2. https://doi.org/10.1016/j.jpeds.2018.12.062

Title:

Assessment of Brain Injury and Brain Volumes after Posthemorrhagic Ventricular Dilatation: A Nested Substudy of the Randomized Controlled ELVIS Trial

Short title:

Time of Intervention in PHVD and Effect on MRI

Authors:

Mehmet N. Cizmeci, Nadieh Khalili, Nathalie H.P Claessens, Floris Groenendaal, Djien Liem, Axel Heep, Isabel Benavente Fernandez, Henrica van Straaten, Gerda van Wezel-Meijler, Jeroen Dudink, Ivana Išgum, Andrew Whitelaw, Manon JNL Benders, Linda S. de Vries and the ELVIS study group.

Abstract

Background: There is accumulating evidence showing beneficial effects of early intervention on posthemorrhagic ventricular dilatation (PHVD) and neurologic outcomes.

Objective: To compare the effect of early and late intervention for PHVD on brain injury and ventricular volume using term-equivalent age magnetic resonance imaging (TEA-MRI).

Methods: In the ELVIS (Early versus Late Ventricular Intervention Study) trial 126 preterm infants ≤34 weeks gestation with PHVD after grade III-IV intraventricular hemorrhage were randomised to low threshold (LT, ventricular index (VI) > p97 and anterior horn width (AHW) > 6mm) or higher threshold (HT, VI > p97 + 4mm and AHW > 10mm). The Kidokoro Global Brain Abnormality Score and the frontal and occipital horn (FOH) ratio were measured. Automatic segmentation was used to perform volumetric measurements.

Results: Of the 110 surviving infants, TEA-MRI was obtained in 88 (80%) infants, of which 44 were in the LT group and 44 in the HT group. The total Kidokoro score of the infants in the LT group was lower

than in the HT group (median (interquartile range): 8 (5-12) vs 12 (9-17), respectively; p<0.001). When the groups were compared in terms of severity of the Kidokoro score, there were more infants in the LT group with a normal or mildly increased score, and more infants in the HT group with a moderately or severely increased score (46% vs. 11% and 89% vs. 54%, respectively; p=0.002). The FOH ratio was lower in the LT group, when compared with the HT group (0.42 (0.34-0.63) vs 0.48 (0.37-0.68), respectively; p=0.001). The ventricular CSF volumes were calculated in 47 infants and were smaller in the LT group (p=0.03).

Conclusion: Our findings demonstrate more brain injury and larger ventricular CSF volumes in the HT group. These results contribute to the growing evidence for the positive effects of early intervention for PHVD.

Keywords: MRI; newborn; posthemorrhagic ventricular dilatation

Introduction

Over the past decades, substantial developments in obstetric and neonatal care have resulted in a significant increase in the survival of premature infants. Along with mortality, a further aim has been to reduce the major morbidities and improve neurodevelopmental outcome. However, due to the increased survival rate of extremely preterm infants, germinal matrix-intraventricular hemorrhage (GMH-IVH) continues to be a serious complication of preterm birth.[1,2] Posthemorrhagic ventricular dilatation (PHVD) occurs in approximately 30-50% of the preterm infants after severe hemorrhage and increases the risk of neurocognitive and motor impairments.[3]

Adverse effects of PHVD on the developing newborn brain include white matter injury and decreased volumes of deep gray matter and cerebellum, indicating the importance of timely intervention to restrict these problems as much as possible.[4] After the use of temporizing methods, overall conversion to a permanent shunt varies from 20-65% depending on the time of onset of the intervention.[5] Given the high rates of infection, dysfunction and life-long dependence after VP-shunt insertion, it would be beneficial if

a treatment could reduce the risk of shunt requirement.[6,7] Removing the hemorrhagic CSF by lumbar punctures or taps from a ventricular reservoir may reduce the need for VP-shunt placement, since removal of CSF that contains blood components, protein, and cytokines might re-establish normal CSF circulation.[8] Although, optimum timing of intervention continues to be a matter of debate in the neonatal literature, there is accumulating evidence showing the beneficial effects of early intervention on ventricular dilatation and outcomes.[9,10] In a recent randomized controlled trial (the ELVIS, Early versus Late Ventricular Intervention Study) no significant difference was found for the need for VP-shunt in those treated before or after crossing the 97th centile +4 mm line of the graph of Levene[11]; however, only a small number of infants in both study arms had a VP-shunt inserted, the lowest number reported in the literature so far (19-23%).[5] The aim of the present nested substudy was to compare the extent of injury in different brain regions and brain volumes on term-equivalent age magnetic resonance imaging (TEA-MRI) in patients randomized to the early or late intervention group.

Patients and Methods

Patients

A total of 126 infants participated in the ELVIS trial, a RCT conducted between 2006 and 2016 to compare the effects of low versus high threshold treatment in preterm infants of ≤34 weeks' gestational age with progressive PHVD. Infants were eligible for the RCT when they had an IVH grade III, with or without a periventricular hemorrhagic infarct (PVHI) according to Volpe[12]. They were randomly allocated to either low threshold (LT) group (intervention when an increase in ventricular width according to Levene[11] above the p97 line showing an increase towards the p97+4mm line but without crossing the p97+4mm line, and an increase in diagonal anterior horn width according to Davies et al.[13] above 6 mm towards 10 mm, but not above 10 mm) or high threshold (HT) group (intervention once the ventricular width crossed the p97+4mm line and the anterior horn width was above 10 mm).

Antenatal and perinatal factors including gestational age, birth weight, sex, the severity of hemorrhage, and timing and type of intervention, and postmenstrual age at MRI day were collected for each patient

from the patient files and/or hospital database. Approval from the Research Ethics Boards at each center and informed written parental consent were obtained for all of the patients and for the control infants participating in the study before enrollment into the study.

MRI Acquisition

In all centers MR images were acquired around TEA. A 3.0 Tesla MR system (Philips Healthcare, Best, The Netherlands) using a sense head coil was available at three centers (University Medical Center Utrecht (UMCU), University Medical Center Leiden and Isala Hospital, Zwolle) and from 2014 onwards at Southmead Hospital, Bristol. Until April 2014, a 1.5-Tesla MR system (GE Signa Excite HD system, USA) was used in Bristol. University Medical Center Groningen (SonataVision, Siemens, Germany), University Hospital Puerta del Mar, Cadiz (Magnetom Symphony, Siemens, Germany), Radboud University Nijmegen Medical Centre (Magnetom Symphony, Siemens, Germany), University of Rotterdam (GE Signa Excite HD system, USA) and University of Lisbon (Philips Healthcare, Best, The Netherlands) used a 1.5 Tesla MR system. All participating centers used conventional axial 3D T1-weighted imaging and T2-weighted imaging and followed a predefined MRI protocol according to their institutional guidelines during the study period. Only the high-quality images that were suitable for scoring and volumetric measurements were included in the study.

Assessment of Brain Injury

An investigator with more than 20 years of experience in reading neonatal MRIs (LSdV) who was blinded to the infant's clinical information, and the allocated arm of the RCT, assessed the images. Ventricular measurements, ventricular index (VI) and anterior horn width (AHW), were performed as described by Levene[11] and Davies et al.[13] The frontal and occipital horn (FOH) ratio, was obtained by measuring the widest distances across the frontal horns and the occipital horns, and the average of these measurements was then divided by the largest biparietal diameter as defined by Kulkarni et al.[14] To evaluate the intraobserver reliability of the measurements, 15 studies from 15 random patients were assessed and the intra-class correlation coefficient (ICC) was calculated. For the assessment of brain injury, a validated scoring system for evaluating cerebral white matter (WM) and cortical grey matter (GM) abnormalities

was used. The measurements were corrected for postmenstrual age, and a global brain abnormality score was calculated as the sum of the regional total scores and classified as normal (total score 0-3), mild (total score 4-7), moderate (total score 8-11) and severe (total score 12 or more), as defined by Kidokoro et al.[15]

Assessment of Brain Volumes

Automatic segmentation of cerebral MRIs was applied on axial or coronal T2-weighted images for computerized volume analysis. The images were segmented into 8 regions: cerebellum, myelinated white matter (mWM), basal ganglia and thalami (BGT), ventricular cerebrospinal fluid (vCSF), unmyelinated WM, brain stem, cortical GM, and extracerebral cerebrospinal fluid (eCSF), as described by Moeskops et al.[16] Quality of automatic segmentations was established by visual evaluation. Images with low-quality segmentations were excluded from further analysis, and high-quality images were manually edited when deemed necessary prior to further analysis. Subsequently, volumetric measurements of the segmented tissues were obtained by multiplying the number of segmented voxels per tissue by the voxel size. Thereafter, contours were drawn around the structure of interest on consecutive slices through the brain. Both porencephalic cysts and cysts following PVHI but not communicating with the lateral ventricles were included in ventricular volume measurements. The relative volumes of the brain regions were calculated by dividing the volume of the area of interest by total intracranial volume, which includes brain tissues and ventricular and extra-ventricular CSF spaces (Figure 1).

Statistical Analysis

Statistical analyses of the data were performed using the Statistical Package for the Social Sciences v21.0 program (SPSS Inc., Chicago, Ill., USA). Details of the statistical analysis are presented in Supplement 1.

Results

Study Population

During the 10-year study period, a total of 126 infants were enrolled into the ELVIS cohort of whom 38 were not eligible for inclusion in the present study since no MRI was available around TEA due to either death of the infant (n=16) or logistic reasons (n=22). This resulted in a final sample of 88 infants being enrolled in the study. Of these infants, 44 were in the LT group and 44 were in the HT group (Supplement 2). No statistically significant differences between the LT and HT groups were observed in terms of gestational age, sex, birth weight and postmenstrual age at the time of MRI. Thirty (68%) infants in the LT group had a grade III hemorrhage and 14 (32%) had a PVHI, while 25 (57%) infants had a grade III hemorrhage and 19 (43%) had a PVHI in the HT arm (p=0.3). The time-interval between the VP-shunt insertion and acquisition of the TEA-MRI was similar across the groups. Characteristics of the participants in whom MRI was completed are presented in Table 1.

Frontal and Occipital Horn Ratio and Kidokoro Score

The intra-observer reliability showed an excellent correlation for the measurements (ICC=0.94). Median ventricular measurements, including VI and AHW were significantly lower in the LT group (median (IQR): 13.4 (12.6-15.1) vs 15.9 (14.5-18.8) and 6.6 (5.3-10.3) vs 10.6 (8.4-13.5), respectively; $p<0.001$ for both). The FOH ratio was significantly lower in the LT group when compared with the HT group (0.42 (0.4-0.46) vs 0.48 (0.43-0.51), respectively; p=0.001). The total Kidokoro score of the infants in the LT group was significantly lower than that of the HT group (8 (5-12) vs 12 (9-17), respectively; $p<0.001$). When the groups were compared in terms of severity of the Kidokoro score, there were significantly more infants in the LT group with a normal or mildly increased score and more infants in the HT group with a moderately or severely increased score ($p<0.001$, Table 1). Observed associations persisted after controlling for the grade of IVH. A significant linear correlation between the Kidokoro score and FOH ratio was found (r=0.62, $p<0.001$) and average FOH ratio increased by 0.06 for every point increase in the Kidokoro score (95% confidence interval (CI): 0.05-0.08).

Kidokoro Subscores

In the cerebral white matter (WM) evaluation, statistically significant differences were observed between the groups in myelination delay, thinning of the corpus callosum and dilatation of the lateral ventricles subscores. Furthermore, a trend towards biparietal volume reduction in the HT group was seen (p=0.07). The groups were different with regards to cerebral WM subscore (p=0.001). In the cortical GM evaluation, infants in the HT arm showed increased extra-cerebral spaces (p<0.001) and a trend towards delayed gyral maturation (p=0.07). The cortical and BGT subscores were lower in the LT group (p<0.001). The groups were similar in terms of cerebellar signal abnormalities and volume reduction (p=0.8 and p=0.4, respectively). The subscore analysis of the infants are tabulated in Table 2.

Brain and CSF Volumes on TEA-MRI

Brain and CSF volumes were calculated in a total of 47 infants, of which 21 were in the LT and 26 in the HT group (Supplement 2). No statistically significant differences in unadjusted brain and CSF volumes were observed in relation to PHVD (Table 3). When the relative volumes of the brain regions were compared after normalization of the variables with logarithmic transformation, ventricular CSF volumes of the LT group were lower than that of the HT group (p=0.03) (Figure 2). Unmyelinated WM volume of the LT group was larger than that of the HT group, but this was not statistically significant (p=0.2). Combination of the WM and GM volumes showed a trend towards increase in the LT group when compared with the HT group (p=0.06). In the subgroup analysis, after excluding infants with PVHI, GM volume showed a trend towards increase (p=0.06), and combination of the WM and GM volumes were significantly higher in the LT group (p=0.03). There were no differences between groups in other regions of interest. The FOH ratio was positively associated with ventricular CSF volumes (β [95% CI]: +145 [72; 218], p<0.001).

Discussion

In this nested substudy of our recently published randomized controlled ELVIS trial[5] of preterm infants with PHVD, infants who were in the LT group had lower global brain abnormality scores and had lower regional total subscores of the cerebral WM, cortical GM and BGT on TEA-MRI. When the total Kidokoro scores were stratified according to the severity, there were significantly more infants with normal or mildly increased scores in the LT group, and significantly more infants with moderately or severely increased scores in the HT group, even though at the time of randomization the number of infants with a grade III hemorrhage or PVHI was similar in the study arms. Infants in the HT group also demonstrated a delay in myelination and more often partial or global thinning of the corpus callosum. Moreover, lower FOH ratios, VI and AHW at TEA and smaller ventricular CSF volumes were found in infants in the LT group. In the subgroup analysis, after excluding infants with PVHI, combination of the WM and GM volumes was significantly higher in the LT group ($p=0.03$). Using a structured scale assessment together with the quantification of the ventricular dilatation acquired at TEA, we were able to identify injury in specific regions of the brain demonstrating the possible beneficial effects of early intervention after the onset of PHVD.

The pathogenesis of PHVD is a complex process determined by both direct injury and secondary inflammatory interactions.[17-21] To address the net effects of PHVD on brain lesions in different regions, an objective structured scale assessment was used in combination with volumetric analysis in the present study. This approach enabled us to determine the correlation between ventricular size and the extent of brain injury. The smaller ventricular CSF volumes together with the lower global brain abnormality scores as well as lower regional total subscores of the major regions of the brain in the LT group demonstrates the possible beneficial effects of early intervention as we found that almost half (46%) of the infants in the LT group had normal or mildly increased Kidokoro scores compared with only 11% in the HT group. In infants with PHVD, expanding ventricles might cause atrophy of the adjacent brain tissue as a result of compression by CSF under pressure and impaired BGT hemodynamics.[22,23] By using

a manual segmentation technique, Jary et al.[22] calculated cerebral, thalamic and cerebellar volumes, and demonstrated that brain growth is significantly impaired in PHVD. Ventricles were larger with a median volume of 48 cc (IQR: 27-145) than the ventricular volumes of both groups in our study (median volume: 18 cc and 24 cc in LT group and HT group, respectively). Brouwer et al.[4] reported data in a small group of infants and showed that PHVD was independently associated with decreased volumes of deep GM, cerebellum and extracerebral CSF, despite early intervention. They found a median ventricular volume of 18.3 cc (range: 8.6 - 64.5) in infants with PHVD, which is lower than we report in the HT group and overlaps considerably with values we found in the LT group. It has been shown that in infants with severe IVH who developed PHVD, ventricular size may be an important determinant of long-term neurodevelopmental outcome and infants with severe IVH who developed PHVD had worse neurodevelopmental scores compared with those who did not develop PHVD.[12,24,25] Recently, Leijser et al.[10] reported in their large cohort of preterm infants with PHVD that those who underwent intervention based on ventricular measurements, prior to the development of symptoms, even when eventually requiring a VP-shunt, had outcomes indistinguishable from those without intervention, all being within the normal range. Infants who first received intervention once clinical symptoms had occurred had worse outcomes. The volumes of the ventricles, and combined volume of the unmyelinated WM and GM regions were in favor of the LT therapy in the present study. We also measured the VI and AHW on TEA-MRI, which revealed smaller lateral ventricles in the LT group. Whether the smaller ventricular volumes, and preserved unmyelinated WM and GM volumes of infants who underwent LT therapy will be associated with improved neurodevelopmental outcomes in the ELVIS trial is being assessed.

The higher Kidokoro scores in infants in the HT group are in line with the accumulating literature suggesting that progressive ventricular dilatation and prolonged pressure might be deleterious to the immature brain. A rapidly enlarging ventricular system could result in the compression of the adjacent brain parenchyma and this has been used as an explanation for the MRI signal abnormalities in various regions of the brain.[26,27] Since infants in the HT group had larger ventricular volumes than those of the LT

group, the Kidokoro scores of these infants, which increase directly with the presence of signal abnormalities could have increased. PHVD-induced microstructural white matter injury, as stated previously by Brouwer et al.[4], might serve as another explanation for the signal abnormalities on TEA-MRI in our cohort. It is also worth noting that FOH ratios showed good correlation with ventricular volumetric measurements, which can be used as a practical assessment tool for calculating the ventricular volumes in patients with PHVD.

The present study has several limitations. First, MRI protocols were not the same across centers. Second, a relatively large number of segmented MRIs could not be used for the volumetric analysis due to insufficient image quality. Third, our automatic segmentation method did not allow differentiation between the basal ganglia and thalamic volumes and could not demonstrate precise segmentation of myelinated white matter due to technical reasons. The main strength of the study was the use of an objective scoring system enabling assessment of the extent of brain injury and reliable quantification of the ventricular and brain volumes in a sufficient number of infants.

Today, PHVD remains a serious complication of IVH, and control of PHVD using LPs before or just after the VI crossed the p97 + 4mm line was associated with the lowest need for VP shunt reported in the literature, according to the ELVIS trial.[5] This nested substudy of the ELVIS trial, designed to address parenchymal injury in different regions of the brain together with the quantification of the CSF and brain volumes, demonstrates beneficial effects of early intervention on the extent of brain injury and ventricular CSF volumes. Whether these findings translate into improved neurological development is being assessed and will be the subject of a later report.

Acknowledgement

The authors have no financial relationship or any other conflict of interest to declare. The authors thank the MR technicians for their dedicated help to obtain the MR images.

References

1. Stoll BJ, Hansen NI, Bell EF, et al. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012. JAMA 2015;314:1039-51.
2. Ellenbogen JR, Waqar M, Pettorini B. Management of post-haemorrhagic hydrocephalus in premature infants. J Clin Neurosci 2016;31:30-4.
3. Adams-Chapman I, Hansen NI, Stoll BJ, Higgins R, Network NR. Neurodevelopmental outcome of extremely low birth weight infants with posthemorrhagic hydrocephalus requiring shunt insertion. Pediatrics 2008;121:e1167-77.
4. Brouwer MJ, de Vries LS, Kersbergen KJ, et al. Effects of Posthemorrhagic Ventricular Dilatation in the Preterm Infant on Brain Volumes and White Matter Diffusion Variables at Term-Equivalent Age. J Pediatr 2016;168:41-9 e1.
5. de Vries LS, Groenendaal F, Liem KD, et al. Treatment thresholds for intervention in posthaemorrhagic ventricular dilation: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2018.
6. Wellons JC, 3rd, Shannon CN, Holubkov R, et al. Shunting outcomes in posthemorrhagic hydrocephalus: results of a Hydrocephalus Clinical Research Network prospective cohort study. J Neurosurg Pediatr 2017;20:19-29.
7. Hislop JE, Dubowitz LM, Kaiser AM, Singh MP, Whitelaw AG. Outcome of infants shunted for post-haemorrhagic ventricular dilatation. Dev Med Child Neurol 1988;30:451-6.
8. Cherian S, Whitelaw A, Thoresen M, Love S. The pathogenesis of neonatal post-hemorrhagic hydrocephalus. Brain Pathol 2004;14:305-11.
9. Bassan H, Eshel R, Golan I, et al. Timing of external ventricular drainage and neurodevelopmental outcome in preterm infants with posthemorrhagic hydrocephalus. Eur J Paediatr Neurol 2012;16:662-70.
10. Leijser LM, Miller SP, van Wezel-Meijler G, et al. Posthemorrhagic ventricular dilatation in preterm infants: When best to intervene? Neurology 2018;90:e698-e706.
11. Levene MI. Measurement of the growth of the lateral ventricles in preterm infants with real-time ultrasound. Arch Dis Child 1981;56:900-4.
12. J V. Intracranial Hemorhage: Germinal Matrix-Intraventricular Hemorrhage of the Premature Infant. Neurology of the Newborn. Philadelphia: Saunders Elsevier; 2008:517-88.
13. Davies MW, Swaminathan M, Chuang SL, Betheras FR. Reference ranges for the linear dimensions of the intracranial ventricles in preterm neonates. Arch Dis Child Fetal Neonatal Ed 2000;82:F218-23.
14. Kulkarni AV, Drake JM, Armstrong DC, Dirks PB. Measurement of ventricular size: reliability of the frontal and occipital horn ratio compared to subjective assessment. Pediatr Neurosurg 1999;31:65-70.
15. Kidokoro H, Neil JJ, Inder TE. New MR imaging assessment tool to define brain abnormalities in very preterm infants at term. AJNR Am J Neuroradiol 2013;34:2208-14.
16. Moeskops P, Viergever MA, Mendrik AM, de Vries LS, Benders MJ, Isgum I. Automatic Segmentation of MR Brain Images With a Convolutional Neural Network. IEEE Trans Med Imaging 2016;35:1252-61.
17. Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol 2009;8:110-24.

18. Savman K, Blennow M, Hagberg H, Tarkowski E, Thoresen M, Whitelaw A. Cytokine response in cerebrospinal fluid from preterm infants with posthaemorrhagic ventricular dilatation. Acta Paediatr 2002;91:1357-63.
19. Whitelaw A, Cherian S, Thoresen M, Pople I. Posthaemorrhagic ventricular dilatation: new mechanisms and new treatment. Acta Paediatr Suppl 2004;93:11-4.
20. Srinivasakumar P, Limbrick D, Munro R, et al. Posthemorrhagic ventricular dilatation-impact on early neurodevelopmental outcome. Am J Perinatol 2013;30:207-14.
21. Tam EW, Miller SP, Studholme C, et al. Differential effects of intraventricular hemorrhage and white matter injury on preterm cerebellar growth. J Pediatr 2011;158:366-71.
22. Jary S, De Carli A, Ramenghi LA, Whitelaw A. Impaired brain growth and neurodevelopment in preterm infants with posthaemorrhagic ventricular dilatation. Acta Paediatr 2012;101:743-8.
23. Soul JS, Taylor GA, Wypij D, Duplessis AJ, Volpe JJ. Noninvasive detection of changes in cerebral blood flow by near-infrared spectroscopy in a piglet model of hydrocephalus. Pediatr Res 2000;48:445-9.
24. Resch B, Gedermann A, Maurer U, Ritschl E, Muller W. Neurodevelopmental outcome of hydrocephalus following intra-/periventricular hemorrhage in preterm infants: short- and long-term results. Childs Nerv Syst 1996;12:27-33.
25. van Zanten SA, de Haan TR, Ursum J, van Sonderen L. Neurodevelopmental outcome of post-hemorrhagic ventricular dilatation at 12 and 24 months corrected age with high-threshold therapy. Eur J Paediatr Neurol 2011;15:487-92.
26. McClain C.D SSG. Principles of paediatric neurosurgery. In: Matta B.F MDK, Smith M., ed. Core Topics in Neuroanaesthesia and Neurointensive Care: Cambridge University Press; 2011:205-21.
27. Mokri B. The Monro-Kellie hypothesis: applications in CSF volume depletion. Neurology 2001;56:1746-8.